The FDA Critical Path Initiative and Its Influence on New Drug Development*

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Abstract

Societal expectations about drug safety and efficacy are rising while productivity in the pharmaceutical industry is falling. In 2004, the US Food and Drug Administration introduced the Critical Path Initiative with the intent of modernizing drug development by incorporating recent scientific advances, such as genomics and advanced imaging technologies, into the process. An important part of the initiative is the use of public-private partnerships and consortia to accomplish the needed research. This article explicates the reasoning behind the Critical Path Initiative and discusses examples of successful consortia.

INTRODUCTION

In 2004, the US Food and Drug Administration (FDA) launched the Critical Path Initiative, a project that is intended to improve the drug and medical device development processes, the quality of evidence generated during development, and the outcomes of clinical use of these products. Why would a regulatory agency be involved in such a modernization effort? FDA's mission is to protect and promote the health of the public. With respect to drugs, biological products, and medical devices, this translates into ensuring reasonable product safety while also facilitating the translation of scientific innovations into commercial products. The ongoing tension between these two objectives results in assertions that FDA requirements are stifling innovation, and simultaneously that FDA standards are too low. The thesis of the Critical Path Initiative is that scientific advances in the development process are the best way to resolve these conflicts to the satisfaction of most parties and to the benefit of the public. Although the initiative concerns all regulated medical products, this review discusses Critical Path in the context of drug development.

BACKGROUND

Rising Expectations about Drug Development

In 1962, congressional amendments to the Food, Drug, and Cosmetic Act created for the first time a requirement that drugs be scientifically shown to be effective before they could be marketed (a requirement for safety had been in effect since 1938). During the 1960s–1980s, drug developers, the academic community, and regulators worked to develop and refine ways to design, conduct, and analyze randomized controlled clinical trials that could produce the needed evidence. Many important advances in pharmacotherapy (e.g., cardiovascular therapies, psychiatric drugs, anti-infectives, and cancer treatments) were introduced during this era. However, the evidence generated in drug development programs was still somewhat limited. For example, dose-response information was usually scanty, often few women were studied, data on long-term use (even for chronically administered drugs) were lacking, evaluations of subgroups such as patients with renal or hepatic insufficiency were not conducted, and data on drug-drug interactions were not available. From the mid-1980s through the 1990s, as an increasing number of drug therapies became available, the FDA as well as the international regulatory community established the expectation that such information would be obtained during most drug development programs. Therefore, modern development programs usually are much more extensive and contain many more clinical studies and patient exposures than was usual in 1960–1985.

Despite these advances, there remains a great deal of uncertainty about the performance of drugs that are new to the market. Data from long-term use are still usually limited. Current drug development programs cannot detect drug-related adverse outcomes that represent a small increase in frequency of a problem that is already common in the treated population (e.g., ischemic cardiovascular events). Technologies to predict the occurrence of rare, catastrophic side effects are not available. Additionally, despite attempts to make the results of clinical trials more generalizable, the patients enrolled in trials do not reflect the full range of the population or treatment situations that occur in practice. As a result, new safety issues are often identified only after drugs enter the market.

Nevertheless, in the past decade, aggressive marketing techniques have led to immediate uptake and widespread use of many new drugs, combined with a general expectation that their performance is well understood over a wide range of clinical situations. In particular, many members of the public believe that if prescription products are advertised on television, they must be safe. The increasing

recognition of this problem has led to calls for larger trials and longer patient exposures prior to drug marketing.

Not only drug development but also medical practice has become increasingly complex since the 1962 amendments. For many diseases, multiple subgroups and disease stages have been defined, and numerous therapeutic options exist. Drug development programs are rarely designed to answer the questions posed by evidence-based medicine and by insurers: What therapeutic option has the best outcomes in various patient groups or, similarly, what option provides the best value? If comparative trials are performed premarket, they usually involve a demonstration of "noninferiority" in comparison with a single control drug. Increasingly, members of the health care community, as well as Congress, are calling for more of this information to be developed.

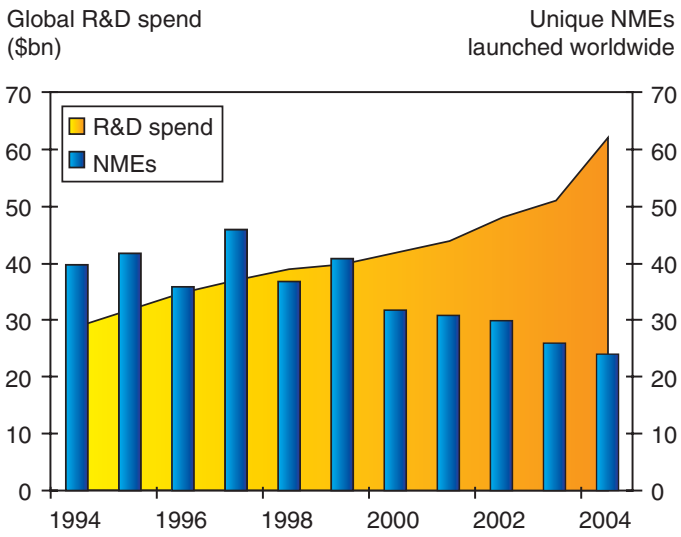

Figure 1

Comparison of global pharmaceutical industry research and development investment and global output of new molecular entities. Source: Hoekema A. 2007. Sharing risks and rewards—basis for a turnkey pharma-biotech alliance in osteoarthritis. *Drug Disc. World* Spring:54

Problems with the Pharmaceutical Pipeline

The pharmaceutical industry is facing a productivity crisis. Despite rising investment in pharmaceutical research and development, successful development of novel drugs is slowing (**Figure 1**). In fact, 2004 represented a 20-year low in introductions of new chemical entities (NMEs) worldwide (1). The same phenomenon has been observed in the United States, where the submission rate of new drug applications for NMEs has shown a downward trend in the past decade (2). Not surprisingly, the investment needed per successful NME has risen to an estimated $800 million or more (3, 4). This cost is driven by the high rate of clinical failure, estimated at 70%–90% of candidates (5). The rising percentage of late-stage clinical failures, now ~50% of compounds tested in phase 3 trials, is of particular concern. The high cost of successful drug development may discourage investment in more innovative, risky approaches, as well as in therapeutics for diseases that represent smaller markets. Additionally, the need to recoup this investment during the period of market exclusivity, prior to the introduction of generic copies, is an incentive for aggressive marketing techniques (6). However, rapid market uptake means that a large number of individuals may have already been exposed by the time a drug problem is discovered after marketing.

Thus, rising societal demands for greater certainty about the outcomes of drug therapy are occurring at a time when the pharmaceutical industry is experiencing difficulty in sustaining innovation. These concurrent trends are a cause for significant concern, given the number of medical conditions that currently have unsatisfactory or no therapeutic options. The FDA, with its dual roles of protecting and promoting health, is charged with implementing policies that ensure that the benefits of new products will outweigh their risks, while simultaneously promoting innovations that can improve health. The challenges inherent to this mission drove the genesis of the Critical Path Initiative.

FDA'S CRITICAL PATH INITIATIVE

Expectations have been widespread that 30 years of significant public investment in biomedical research would produce an explosion of new therapies for previously untreatable or inadequately treated diseases. The failure of this surge to materialize has prompted extensive speculation on the cause of this "pipeline problem." Many in the drug development community believe that genomics and other newer technologies are not yet sufficiently mature to reliably support drug development. Others blame industry business decisions or regulatory requirements. In 2004, the FDA published a White Paper entitled "Innovation or Stagnation: Challenges and Opportunities on the Critical Path to Medical Product Development" (7). While acknowledging that a combination of factors has likely led to the current drug development situation, this paper called attention to an important and generally unrecognized problem: the lagging science of drug development.

Drug development can be conceptualized as a process leading from basic research through a series of developmental steps to a commercial product (**Figure 2**). The FDA White Paper identified the "Critical Path" as a process beginning with identification of a drug candidate and culminating in marketing approval. Along the path to marketing, the product is subjected to a series of evaluations to predict its safety and effectiveness and to enable its mass production. Despite extensive investment in basic biomedical science over the past three decades, there has been very little change in the science of the development process. The sophisticated scientific tools used in drug discovery and lead optimization are generally not utilized in the preclinical and clinical development stages. Instead, traditional empirical evaluation is used in both animal and human testing. We are

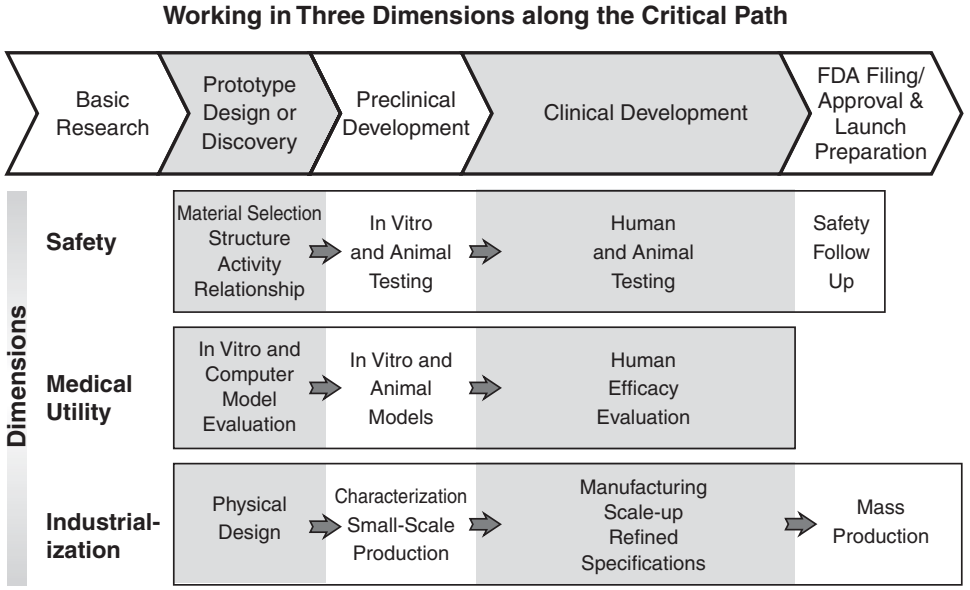

Figure 2

The critical path of drug development. First, a candidate drug emerges from a drug discovery program. The candidate must successfully complete a series of evaluations of its potential safety and efficacy and must be amenable to mass production. For each candidate finishing the pathway, 5000–10,000 are evaluated in the discovery phase.

using the tools of the last century to evaluate this century's advances.

How did this situation come about? The FDA's analysis, which has been generally accepted, is that "no one is charged" with improving developmental science. The National Institutes of Health (NIH) focus on innovative biomedical science, not the applied science of the development process; as a result, academia also concentrates on basic science. The pharmaceutical industry is concerned with developing innovative products. The FDA, as a regulator, is not charged with—nor is it funded for—improving the process, although it has been involved in such efforts. Additionally, the science needed is generally integrative "big science" that requires contributions from multiple disciplines and sectors and is not within the purview of a single investigator or firm.

How is the evaluative science of development related to "translational science"? Translational science, which is also called "experimental medicine," or simply "clinical pharmacology" in the case of drug development, involves moving a scientific innovation from the laboratory into early clinical studies (8). Improvement in this part of the process is an essential step in modernizing drug development.

THE CRITICAL PATH PROGRAM

FDA's 2004 Critical Path White Paper generated considerable discussion and debate among drug and device developers, academics, and patient advocacy groups. Over 100 groups submitted comments on the paper. After extensive consultation with numerous stakeholders, FDA issued the "Critical Path Report and List" in 2006 (9). This report enumerated leading areas for scientific improvement in the development process: development and utilization of biomarkers; modernizing clinical trial methodologies and processes; the aggressive use of bioinformatics, including disease modeling and trial simulation; and improvement in manufacturing technologies. It also contained the "2006 Critical Path Opportunities List," 76 discrete projects that, if completed, could improve product development and subsequent use. A number of these projects are now being undertaken, many in partnership with FDA (10).

Development and Qualification of New Biomarkers

Development of new biomarkers was identified as the highest priority for scientific effort. Genomic, proteomic, and metabolomic technologies, as well as advanced imaging techniques, hold tremendous promise for generating new biomarkers that can reflect the state of health or disease at the molecular level (11). Although much prior discussion about the use of biomarkers in drug development has focused on surrogate endpoints for effectiveness, most uses of new biomarkers are not expected to involve surrogacy. For example, prediction of adequate safety is an essential part of drug development. Currently, preclinical safety testing involves traditional animal toxicology studies, as well as in vitro assays such as the Ames test. Animal toxicology tests are very useful for assessing safety for initial human testing; however, they often fail to uncover the types of toxicities seen after widespread human exposure. New technologies, such as gene expression assays in whole cell or animal systems, proteomics, or metabolomics, may provide much greater insight into the whole spectrum of pharmacologic effects of a candidate drug. Such technologies may also be useful in comparing the candidate's effects (particularly off-target effects) to those of other drugs in its class or other drugs intended for similar uses (12). Drug developers are just beginning to use such technologies in the preclinical safety workup, and the clinical implications of such findings have not been worked out.

The current scheme for clinical safety testing has also failed to incorporate recent scientific advances. Human safety during drug development is primarily evaluated on an

observational basis from subjects exposed in the various developmental trials. The markers used to assess potential human toxicity are also assays that have been available for decades, e.g., clinical chemistries and hemograms. Few explanatory studies are carried out to determine the mechanism of an observed side effect, and assays to predict rare side effects are not available. Despite premarket exposure of thousands of subjects, serious side effects are frequently uncovered after marketing. New types of biomarkers may provide opportunities for prevention or early detection of these adverse events.

The current problems with predicting and evaluating drug efficacy could also be ameliorated by using biomarkers. Many drug efficacy problems stem from the extreme variability of human disease response. New biomarkers can improve diagnosis, define disease subsets that may differ in response, define individual variability in the drug's molecular target, and provide an early readout of response to therapy (11). For example, both in vitro diagnostics and imaging techniques are expected to provide additional information about disease subsets. This is already beginning to happen in cancer, where gene expression assays are being used to supplement histologic and clinical assessments of tumors, e.g., evaluating the likelihood of recurrence and the need for adjuvant therapy. For disorders such as psychiatric conditions that are currently diagnosed by clinical symptoms, it is hoped that genetic or imaging markers may help to distinguish biologically based subsets. A related type of biomarker is one used to predict treatment responsiveness. Many new cancer therapies target a specific molecule or cellular pathway. Genetic, proteomic, or other molecular assays that assess target status within a tumor may be used to predict responsiveness to a targeted drug. This is the strategy used with the drugs trastuzumab (Herceptin®) and imatinib (Gleevec®). Interindividual drug target heterogeneity due to genetic polymorphisms may be important in diseases other than cancer. Using biomarkers to classify patients by disease type or response probability can improve drug development by reducing variability and increasing the size of the treatment effect. If the biomarkers are then incorporated into clinical practice, clinical variability can also be reduced.

Decreasing interindividual differences in drug exposure is another strategy to reduce response variability. Recently, FDA has approved a number of assays for genetic polymorphisms in drug-metabolizing enzymes. Many marketed drugs are subject to polymorphic metabolism, leading to a wide range of exposures in the treated population (13). The safety and effectiveness of these drugs, as well as investigational drugs with variable metabolism, could be improved by using dose adjustments directed by genetic tests.

The absence of practical processes to establish the clinical significance of a given biomarker has severely limited the use of existing biomarkers in drug development and the clinic. The return on investment for diagnostic test manufacturers is seldom sufficient to enable extensive clinical trials, and investigational drugs are rarely developed in concert with new diagnostic tests. To address these issues, FDA and other stakeholders have established the concept of biomarker qualification, which means determining the clinical significance of the biomarker in a specific context (14). For example, a genetic test might be qualified to identify a subset of disease for the purpose of trial enrollment. The quantity of data needed for qualification depends on the intended use, and most uses require far less data than would be required to establish a surrogate endpoint for efficacy.

Because the development and qualification of new biomarkers will benefit many parties, consortia have been formed for this purpose. "The Biomarker Consortium" (**http://www.biomarkersconsortium.org**) at the Foundation for NIH (FNIH) is a leading example. Initiated by federal partners NIH, FDA, and Center for Medicare and Medicaid Services (CMS), along with private sector organizations PhRMA (the pharmaceutical

manufacturers' trade organization) and BIO (the Biotechnology Industry Organization), the consortium now has multiple industrial, academic, and patient group members. It is funding biomarker qualification trials for fluorodeoxyglucose-positron emission tomography (FDG-PET) scanning in non-Hodgkin's lymphoma and lung cancer and is evaluating a number of additional proposals.

CLINICAL TRIAL MODERNIZATION

Other areas in urgent need of improvement are the design, conduct, and analysis of clinical trials during drug development. This part of the Critical Path Initiative includes establishing standards for clinical trial data and its management; fully automating trial process and data management; improving the clinical trial quality management system; and modernizing FDA oversight of the clinical trial process. Significant progress in data standardization has been achieved by the clinical trial standards organization, the Clinical Data Interchange Standards Consortium (CDISC) (**http://www.cdisc.org**). Working with the National Cancer Institute (NCI), FDA has adopted a number of CDISC standards for regulatory submissions. Currently, a CDISC initiative called Clinical Data Acquisitions Standards Harmonization (CDASH), organized to develop standards for case report forms, is ongoing (15). Additionally, FDA is working with the NIH to harmonize and simplify various investigator reporting requirements. Over the past several years, FDA has been modernizing its oversight of clinical trials, has held several public meetings, and has issued guidance and draft regulations. Many parties are interested in improving the consistency, quality, and reliability of clinical trials while reducing the paperwork burdens (16). Discussions about forming a public-private partnership to accomplish these objectives are also ongoing.

BIOINFORMATICS

One of the greatest scientific flaws in the current process of medical product development is its failure to produce generalized knowledge despite a huge investment in data generation. For example, FDA holds the world's largest collection of animal test data and correlated human trial data, but most of this information is unusable in its current form, except to document a specific development program. As a result, opportunities for major improvement are missed. Under the Critical Path Initiative, stakeholders are beginning to take advantage of these opportunities. For example, FDA and various partners have created a standard for a digital electrocardiogram (ECG) recording, and FDA requested that ECG data submitted to it be in this format. At the same time, a data warehouse to hold the ECG data was established. Since that time, >500,000 digital ECGs have been added to the warehouse, and a collaboration with Duke University has been established for overall data analysis (17). This resource may help scientists efficiently evaluate candidate drugs for adverse cardiac repolarization effects, a concern that is currently addressed (somewhat less than satisfactorily) by extensive clinical testing. As data standards for regulatory submissions are implemented, processes and protocols to utilize the data for research purposes without compromising proprietary interests need to be developed.

One important use of such data will be to construct quantitative models of disease processes, incorporating what is known about biomarkers, clinical outcomes, and the effects of various interventions. These models can then be used for trial simulations, to better design appropriate trials and clinical outcome measures (18). Although the FDA has constructed several disease models, this work is in its early stages and will require extensive partnerships. However, there is little doubt that such quantitative approaches constitute the future of product development and assessment.

DRUG MANUFACTURING

Perhaps surprisingly, the manufacturing of pharmaceuticals suffers from the problems of drug development in general. Many drug manufacturing processes are characterized by inefficiency, waste, and neglect of modern process control technologies. Thus, the pharmaceutical manufacturing sector would also benefit from incorporation of new science and technology. FDA is spearheading these changes through its Pharmaceutical Quality for the 21st Century Initiative (19).

CONSORTIA INVOLVED IN CRITICAL PATH ACTIVITIES

After FDA's 2004 call for public-private collaborations, scientists at several universities created programs to work with FDA to conduct the needed research. Despite limited funding, these programs have been able to make significant progress addressing projects called for in the 2006 Critical Path Opportunity List. Investments in programs created by the University of Arizona, Duke University, Massachusetts Institute of Technology (MIT), and the University of California at San Francisco are beginning to produce results (see Sidebar).

The first to respond, the University of Arizona, offered to create a nonprofit research and education institute dedicated solely to work with FDA on the Critical Path Initiative. The Arizona community (state and local governments, business, and philanthropic groups) saw this opportunity to partner with FDA as a way to leverage the state's $2 billion investment in biotechnology. In early 2004, with a planning grant from the state, the FDA, the University of Arizona, and SRI International (a nonprofit corporation, formerly Stanford Research Institute) agreed to create the Critical Path Institute (C-Path). C-Path is envisioned as a neutral third party, without financial support from the regulated industry. Because of C-Path's neutral funding and its mission to focus on process, not products, FDA can actively participate in the work without concerns about conflicts of interest. C-Path's strategy is to invite stakeholders to join consortia in which they can work with the FDA to improve the process of medical product development. The University of Arizona and SRI committed "in kind" support, predominantly the time and effort of their scientists. The FDA agreed to participate under a Memorandum of Understanding. C-Path was incorporated in January 2005 and began initial operations in July 2005 with a $10 million, five-year commitment from the City of Tucson, Pima County, regional municipalities, and private foundations in Arizona (**http://www.C-Path.org**). C-Path has approximately 20 employees working with the FDA and industry scientists on the projects listed in **Table 1**. These projects were selected using three specific criteria. The first and essential requirement is that there be champions for the project within the FDA. Also, there must be two or more companies willing to work together on the project, and there must be a source of external funding that is independent of commercial interests. The projects focus on precompetitive aspects of drug development, e.g., preclinical toxicology.

The first consortium formed by C-Path, the Predictive Safety Testing Consortium (PSTC), was announced in March 2006 by Secretary of Health and Human Services Michael Leavitt. Since then, the PSTC has

ACADEMIC CONTRIBUTIONS TO DRUG DEVELOPMENT SCIENCE

The Center for Biomedical Innovation at MIT (CBI), the Center for Drug Development Sciences (CDDS) at the University of California, San Francisco, and the Duke Clinical Research Institute (DCRI) are examples of university-based centers that are making major contributions to the regulatory sciences. Because of their broad access to outstanding scientists in the academic community, they are important resources for companies that are developing medical products, and they train the innovative leaders.

Table 1 C-Path Institute projects (http://www.C-Path.org)

Development gap	C-Path process	C-Path project	Deliverables
Inconsistent technical methods employed across the industry	Create consortium and process for sharing and validation of methods	Predictive Safety Testing Consortium (PSTC)	New FDA guidances to improve and accelerate preclinical safety testing Increased safety of new drugs
Drugs, devices, and diagnostics developed separately. New cancer drugs only 10%–20% effective	Create cross-industry and cross-agency (FDA/NIH/CMS) collaborations to evaluate multiple technologies	Lung cancer diagnostics validation clinical trial with NCI, FDA, and industry	Test to predict lung cancer response Change drug label Model for future drug/diagnostic products
Drugs and diagnostics developed separately. Warfarin side effects cost ~$1 billion/year and only half (2 million) of patients who need warfarin get treatment	Create cross-industry and cross-agency (FDA/NIH/CMS) collaborations to evaluate multiple technologies	Genomic-based dosing for warfarin, clinical trial with NHLBI, FDA, and industry	Reduce adverse events Increase indicated warfarin treatment Change warfarin label: recommend genetic test Model for future pharmacogenetic clinical trials
High failure rate of clinical trials	Create consortium of orphan disease foundations	Create disease model registries (Nieman-Pick C, valley fever, adrenal cancer)	Template for disease model-based clinical trial design and fewer failed drug development programs

grown from an initial eight to 15 global pharmaceutical companies that are sharing their preclinical methods and data for tests of nephrotoxicity, hepatotoxicity, vascular injury, and carcinogenicity. In this consortium, methods developed by one company that appear to best predict drug toxicity are verified by experiments performed by a second company. Over 160 scientists are participating, including 25 scientists from the FDA and its European counterpart, the EMEA, who participate in the meetings and discussions as advisors. The methods that are cross-validated by the companies are expected to eventually provide the scientific basis for regulatory guidance to be issued by the FDA and the EMEA.

A goal of C-Path projects is to integrate new and advanced technologies into medical product development, especially those that accelerate pathways for innovative diagnostic tests and therapies. For example, C-Path's project with the FDA and the University of Utah examines genetic tests for improved warfarin dosage selection. The goal is to provide the scientifically based pathway for simultaneous development of drugs and genetic tests to improve a drug's safety or effectiveness.

Another of C-Path's projects, the Molecular Assays and Targeted Therapeutics (MATT) project, is being conducted by a collaboration among the FDA, the NCI, and the CMS. MATT's goal is to define a more rapid and efficient process for integrated development of drugs, diagnostics, imaging, and other technologies that work together to help patients with cancer. The project is exploring a regulatory path by examining the utility of diagnostics and drugs that could enable targeted therapy of non-small-cell lung cancers that overexpress the epidermal growth factor receptor.

C-Path's Disease Model Registry (DMR) for orphan drugs (i.e., drugs intended for diseases affecting <200,000 persons in the United States) addresses the rising failure rate during the later phases of drug development. The overall goal of this project is to evaluate

methods and technologies that could improve understanding of the natural history of diseases and thereby identify clinical trial designs and methods that are more informative and have a greater chance for success. C-Path is creating the functional infrastructure for DMR and bringing together patients, the FDA's Office of Orphan Product Development, care providers, researchers, foundations, and commercial entities to help generate the data standards and scientific evidence needed to support the efficient testing of new treatments for patients with orphan diseases. This work will also have relevance to personalized medicine because, similar to the situation with orphan diseases, the smaller marker size and the high cost of product development expected for personalized medicine have deterred investment in this new approach. The DMR will serve as a virtual control group, enabling developers to identify the optimal endpoints for clinical trials and thereby increase the likelihood of success in clinical trials. The DMR technology will also make possible online tracking of clinical outcomes, an essential element of newer innovations such as adaptive trial designs.

The novel aspects of these C-Path projects are the core neutral funding and the scientifically qualified team leaders of the consortia. C-Path brings together scientists from highly competitive companies and then maintains a productive environment through modern project management techniques. Continued participation by the consortium members depends on the rewards they receive for the investment of time and effort. These rewards are expected to be science-based regulatory standards enabled by the work of the consortium, which define a development process that has the greatest possible efficiency and safety.

The future of the Critical Path Initiative is increasingly secure because the many stakeholders in medical product development have come to recognize the value of and need for process improvement. They also recognize the importance of having a safe haven such as MIT's Center for Biomedical Innovation or a neutral third party such as C-Path where members of the pharmaceutical industry and the FDA can work as scientists and not be inhibited by their usual roles as regulators and regulated. Likewise, industry scientists are finding it very rewarding to share with their competitors their knowledge and experiences, especially their failures, in precompetitive areas of development. Therefore, it is likely that the work of the critical path will continue indefinitely. What is not yet clear is where it will take place and how it will be coordinated.

The NIH is increasingly involved in critical path projects. The NCI collaborates with the FDA through the Oncology Biomarker Qualification Initiative (OBQI). The National Heart, Lung, and Blood Institute has been working with the FDA to coordinate studies of the genetic testing of warfarin. However, tremendous potential remains for the NIH to play an important role in providing FDA with the data and scientific information needed to improve medical product development. Examples include the NIH roadmap initiatives, the facilities of the National Center for Research Resources, and the growing network of Clinical Translational Research Awards. These are almost all devoted to translational science and have the potential to interface directly with some of the 76 projects on the 2006 Critical Path Opportunities List.

An additional opportunity to maximize the efficiency and impact of critical path research is being explored through increasing collaborations between FDA and Agency for Healthcare Research and Quality (AHRQ) scientists. AHRQ's Centers for Education and Research on Therapeutics are working closely with the FDA to define the optimal approach for active surveillance and postmarketing evaluation of safety and effectiveness of medical products. Ongoing application of new surveillance techniques that are enabled by more widespread use of electronic health records should complement the improved understanding of drugs obtained prior to marketing. It is hoped that electronic records–based surveillance will

result in rapid detection and analysis of unanticipated outcomes after the products are widely used, so that knowledge can be gained efficiently throughout the entire product life cycle.

As of this writing, the US Congress is considering the FDA Revitalization Act. This legislation would create the Reagan-Udall Institute, a foundation established to advance FDA's mission, that would engage in critical path research. Legislation being introduced in the House of Representatives would authorize funding for the FDA to create multiple critical path public-private partnerships. The European Commission is in the final stages of approving the Innovative Medicines Initiative, a partnership among the pharmaceutical industry, the European Union, and academia that would conduct research relevant to drug development, with funding divided equally between government and industry.

The need for critical path research is not likely to end. Scientific advances will continue to create methodological challenges in medicine that will require changes in the way we develop new products. Ideally, a systematic approach to process improvement will become part of the fabric of translational research. A major question is whether the Critical Path Initiative can maintain its momentum and substantively contribute to improved drug development.

SUMMARY POINTS

1. The productivity of the pharmaceutical industry has decreased and the costs of producing a novel medicine have been rising sharply.
2. Some members of the public are calling for medicines to be more extensively studied prior to approval. There is also concern in the United States about pharmaceutical prices.
3. FDA's Critical Path Initiative is intended to improve drug development and reduce uncertainty by applying new scientific tools to the development process.
4. The applied research needed to develop these tools requires collaboration across multiple public and private entities and may be best accomplished by various consortia.
5. The C-Path Institute was set up specifically to facilitate and conduct such research, and it has a number of important projects under way.

DISCLOSURE STATEMENT

Dr. Woodcock directs the Critical Path Initiative at FDA. Dr. Woosley is president of the Critical Path Institute.

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Contents

Indexes

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